Exercise Performance of Lowlanders with COPD at 2,590 m: Data from a Randomized Trial

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Abstract: BACKGROUND Effects of hypobaric hypoxia at altitude on exercise performance of lowlanders with chronic obstructive pulmonary disease (COPD) have not been studied in detail. OBJECTIVES To quantify changes in exercise performance and associated physiologic responses in lowlanders with COPD travelling to moderate altitude. METHODS A total of 31 COPD patients with a median age (quartiles) of 66 years (59; 69) and FEV1 of 56% predicted (49; 69) living below 800 m performed a constant-load bicycle exercise to exhaustion at 60% of the maximal work rate at 490 m (Zurich) and at an identical work rate at 2,590 m (Davos) in randomized order. Pulmonary gas exchange, pulse oximetry (SpO2), cerebral tissue oxygenation (CTO; near-infrared spectroscopy), and middle cerebral artery peak blood flow velocity (MCAv) by Doppler ultrasound during 30 s at end exercise were compared between altitudes. RESULTS With ascent from 490 to 2,590 m, the median endurance time (quartiles) was reduced from 500 s (256; 795) to 205 s (139; 297) by a median (95% CI) of 303 s (150-420) ($p < 0.001$). End exercise SpO2 decreased from 92% (89; 94) to 81% (77; 84) and CTO from 62% (56; 66) to 55% (50; 60); end exercise minute ventilation increased from 40.6 L/min (35.5; 47.8) to 47.2 L/min (39.6; 58.7) ($p < 0.05$; all comparisons 2,590 vs. 490 m). MCAv increased similarly from rest to end exercise at 490 m (+25% [17; 36]) and at 2,590 m (+21% [14; 30]). However, the ratio of MCAv increase to SpO2 drop during exercise decreased from +6%/% (3; 12) at 490 m to +3%/% (2; 5) at 2,590 m ($p < 0.05$). CONCLUSIONS In lowlanders with COPD travelling to 2,590 m, exercise endurance is reduced by more than half compared to 490 m in association with reductions in systemic and cerebral oxygen availability.

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Exercise Performance of Lowlanders with COPD at 2,590 m: Data from a Randomized Trial

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Keywords
Altitude · Chronic obstructive pulmonary disease · Exercise · Hypobaric hypoxia · Physiology

Abstract
Background: Effects of hypobaric hypoxia at altitude on exercise performance of lowlanders with chronic obstructive pulmonary disease (COPD) have not been studied in detail. ***Objectives:*** To quantify changes in exercise performance and associated physiologic responses in lowlanders with COPD travelling to moderate altitude. ***Methods:*** A total of 31 COPD patients with a median age (quartiles) of 66 years (59; 69) and FEV_1 of 56% predicted (49; 69) living below 800 m performed a constant-load bicycle exercise to exhaustion at 60% of the maximal work rate at 490 m (Zurich) and at an identical work rate at 2,590 m (Davos) in randomized order. Pulmonary gas exchange, pulse oximetry (Spo_2), cerebral tissue oxygenation (CTO; near-infrared spectroscopy), and middle cerebral artery peak blood flow velocity (MCAv) by Doppler ultrasound during 30 s at end exercise were compared between altitudes. ***Results:*** With ascent from 490 to 2,590 m, the median endurance time (quartiles) was reduced from 500 s (256; 795) to 205 s (139; 297) by a median (95% CI) of 303 s (150–420) ($p < 0.001$). End exercise Spo_2 decreased from 92% (89; 94) to 81% (77; 84) and CTO from 62% (56; 66) to 55% (50; 60); end exercise minute ventilation increased from 40.6 L/min (35.5; 47.8) to 47.2 L/min (39.6; 58.7) ($p < 0.05$; all comparisons 2,590 vs. 490 m). MCAv increased similarly from rest to end exercise at 490 m (+25% [17; 36]) and at 2,590 m (+21% [14; 30]). However, the ratio of MCAv increase to Spo_2 drop during exercise decreased from +6%/% (3; 12) at 490 m to +3%/% (2; 5) at 2,590 m ($p < 0.05$). ***Conclusions:*** In lowlanders with COPD travelling to 2,590 m, exercise endurance is reduced by more than half compared to 490 m in association with reductions in systemic and cerebral oxygen availability.

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Introduction

Worldwide, millions of persons travel to high altitude for professional or recreational activities and this is generally well tolerated by healthy individuals. In turn, patients with a preexisting lung disease such as chronic obstructive pulmonary disease (COPD) may experience a pronounced exercise limitation at altitude that restricts their daily activities. Near sea level, exercise performance of COPD patients is impaired by dyspnea [1], gas exchange and ventilatory limitations with dynamic hyperinflation [2, 3], muscle weakness [4, 5], and several other factors [6]. The reduced inspiratory pressure of O_2 at higher altitude may aggravate the impairment of exercise performance by inducing hypoxemia and pulmonary vasoconstriction. Further, mechanical ventilatory constraints that impair the response to hypoxemia may combine with additional factors limiting exercise performance, such as cerebral hypoxia, as suggested by studies on healthy subjects [7–9].

In COPD patients, the physiologic effects of altitude exposure have not been studied in detail. Therefore, the purpose of the current study was to quantify the changes in exercise performance in lowlanders with COPD ascending from 490 to 2,590 m and to test the hypothesis that altitude-induced changes in exercise performance are associated with changes in systemic and cerebral availability of oxygen.

Methods

Design

The current data were collected from June to August 2013 from participants in a randomized trial evaluating adverse effects of altitude exposure in COPD patients travelling from 490 to 2,590 m (ClinicalTrial.gov NCT01875133). The patient characteristics were previously reported in abstract form [10, 11]. The data on cardiopulmonary exercise and cerebral blood flow presented here have not been published yet.

Participants

Patients with COPD diagnosed according to the GOLD criteria with severity grades of 2–3 (FEV_1/FVC <0.7 and FEV_1 30–80% predicted), aged 18–75 years (both genders), and residing below 800 m were invited to participate. Exclusion criteria were a resting Sp_{O_2} <92% at 490 m or <80% at 2,590 m right before exercise, any acute intercurrent disease or inadequately controlled cardiovascular disease, and a history of previous stroke or obstructive sleep apnea. Informed written consent was obtained, and the study was approved by the institutional ethics committee of the canton of Zurich, Switzerland (EK-2013-0088).

Interventions

The participants spent 2 days each at 490, 1,650, and 2,590 m (mean barometric pressures [PB] of 720, 626, and 562 mm Hg, respectively). According to the rationale of the main trial, the patients were randomized to one of the following 4 different altitude exposure sequences: (A) 490-1,650-2,590 m; (B) 490-2,590-1,650 m; (C) 1,650-2,590-490 m; and (D) 2,590-1,650-490 m. Due to logistic reasons, the assessments for the current study could only be performed at 490 and 2,590 m. The measurements at 490 m and at the higher altitudes were scheduled 2 weeks apart to let patients recover completely and to allow for washout of any effects of acclimatization. Transfers between locations were made by train (from Zurich to Davos) and cable car (1,650–2,590 m) within 2–5 h.

On the second day, after the first night at 490 and 2,590 m, between 14:00 and 17:00, the patients performed a cycling exercise to exhaustion in a semi-recumbent position (60° head-up; ergoline GmbH, Bitz, Germany). At 490 and 2,590 m, individually identical constant-load protocols were applied with a mean load ± SD of 65 ± 29 W, corresponding to 60% of the maximal work rate assessed by the ramp protocol at 490 m. Baseline measurements were obtained during 5 min at rest on the bicycle. The patients then started cycling at 60 rpm and were encouraged to continue as long as possible. End exercise was defined as a reduction in cycling frequency to <40 rpm.

Measurements

Work rates and breath-by-breath pulmonary gas exchange measures were recorded by a metabolic unit (Ergostick; Geratherm Medical AG, Geschwenda, Germany) according to standard techniques [12]. According to convention, minute ventilation (V'_E) and tidal volume (V_T) were expressed in BTPS (body temperature and pressure, saturated) conditions, and oxygen uptake (V'_{O_2}) and carbon dioxide output (V'_{CO_2}) in STPD (standard temperature and pressure, dry) conditions. To adjust for the increase in V'_E (measured in BTPS) related to the lower PB at 2,590 m, values of ventilatory equivalents adjusted to the PB at 490 m were computed so that the molecular gas flow corresponded to that at 490 m, i.e., V'_E/V'_{CO_2} adj. = $[V'_{E_{2,590m}} \times (PB_{2,590m} - PH_2O)/(PB_{490m} - PH_2O)]/V'_{CO_2}$. Breathing reserve was computed as $40 \times FEV_1 - V'_E$ at end exercise, and the dead-space-to-V_T ratio as $V_D/V_T = [(Pa_{CO_2} - Pet_{CO_2})/Pa_{CO_2}]$ [12]. Breath-by-breath changes in end-expiratory lung volume (EELV) were monitored unobtrusively by calibrated respiratory inductive plethysmography operated in the direct current mode (Respitrace; NIMS, Miami Beach, FL, USA) [13, 14]. The intention was to avoid potential alterations in the natural breathing pattern by repeated inspiratory-capacity maneuvers. Operating lung volumes were calculated as follows: functional residual capacity (FRC) at rest was measured by body plethysmography (see below); EELV over the course of exercise was calculated as FRC + change in EELV over the course of exercise; end-inspiratory lung volume (EILV) was calculated as EELV + tidal volume; inspiratory reserve volume (IRV) was calculated as TLC – EILV. Sp_{O_2}, electrocardiograms, blood pressure, near-infrared spectroscopy (NIRS) images of the frontal brain and quadriceps muscles, and blood flow velocity in the middle cerebral artery (MCA) by transcranial Doppler ultrasound were continuously recorded.

NIRS optodes (NIRO-200NX, Hamamatsu, Japan) were placed bilaterally at the Fp1 and Fp2 landmarks of the 10-10 electrode placement system [15] and bilaterally over the vastus late-

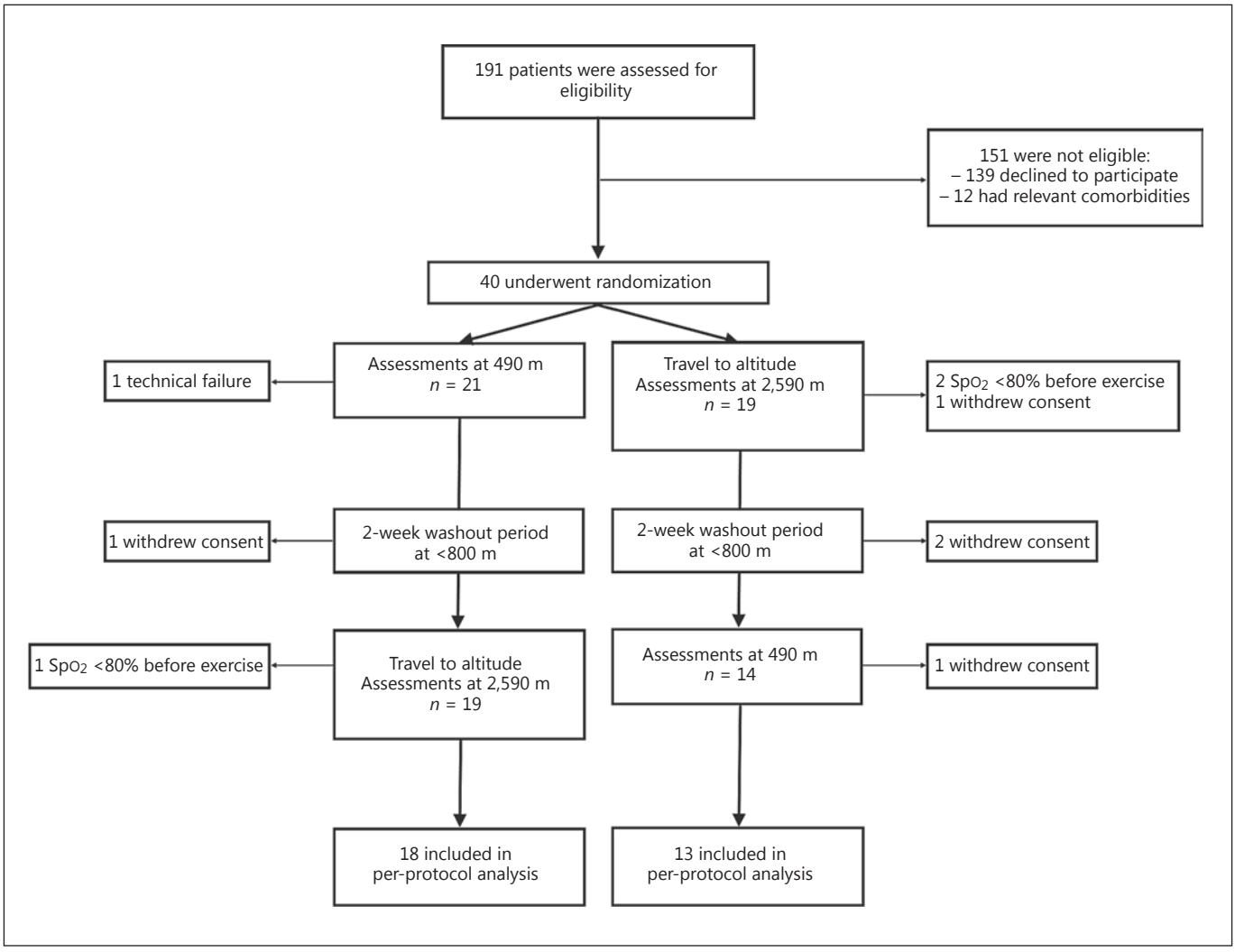

Fig. 1. Patient selection flowchart of the study.

ralis muscles [16]. Mean values of bilateral cerebral (CTO) and bilateral quadriceps muscle (MTO) tissue oxygenation, calculated as the ratio of the oxygenated/oxygenated + deoxygenated hemoglobin concentration, are reported. A 2-MHz ultrasound Doppler probe (TOC2M; Multigon Industries, New York, NY, USA) was placed over the temporal window to record the right MCA peak blood flow velocity (MCAv) [17]. The cerebral blood flow response to the exercise-induced change in Sp_{O_2} was quantified by calculating the ratio of change in MCAv per change in Sp_{O_2}. Continuous blood pressure recordings were obtained by the finger cuff technique (Finometer Midi; Finapres Medical Systems, Amsterdam, The Netherlands). At both altitudes, arterial blood samples were drawn during a resting period before exercise and during the final 30 s of end exercise. Spirometry, body plethysmography, and measurement of single breath diffusing capacity were performed according to standard techniques with the reference values of the Global Lung Function Initiative (GLI) and Quanjer et al. [18–22]. Dyspnea and leg fatigue were rated on the Borg CR10 Scale [23].

Outcomes

The main outcome of this study was the change in cycling endurance between measurements at 490 and 2,590 m. Additional outcomes were changes in physiologic variables.

Data Analysis

The data are summarized as medians and quartiles. Analyses were performed according to the per-protocol approach including data from patients with complete data. Median values of physiologic variables measured during 3 min of quiet rest, during the final 30 s of end exercise, and during the time (isotime) corresponding to the end exercise time in tests with shorter endurance were computed. Paired comparisons were performed by Wilcoxon signed-rank tests and by computing median differences with 95% confidence intervals (CI). Multivariate regression analysis was performed to elucidate whether the order of altitude exposure, baseline endurance, or other baseline variables were independent predictors of exercise endurance at 2,590 m. The outcome assessors were blinded to altitude allocation. A probability <0.05 was considered statistically significant.

Table 1. Patient characteristics

General information		
Subjects (male/female), *n*	31 (19/12)	
Age, years	66 (59; 69)	
Range	51–74	
Body mass index	27.3 (22.0; 29.4)	
Smoking habit		
Current	7	
Former	22	
Never	2	
Smoking, pack-years	40 (20; 60)	
Pulmonary function and oxygen uptake	**at 490 m**	**at 2,590 m**
FVC, L	3.36 (2.63; 4.01)	3.30 (2.87; 4.07)
FVC, % predicted	88 (77; 100)	92 (77; 101)
FEV_1, L	1.69 (1.28; 2.14)	1.76 (1.33; 2.17)
FEV_1, % predicted	56 (49; 69)	53 (48; 66)
FEV_1/FVC, %	52 (46; 63)	55 (46; 64)
FEV_1/FVC, % predicted	66 (58; 80)	70 (57; 81)
TLC, L	6.79 (5.77; 7.79)	
TLC, % predicted	111 (97; 118)	
RV, L	2.94 (2.55; 3.39)	
RV, % predicted	127 (118; 140)	
RV/TLC, %	45 (40; 50)	
FRC, L	4.36 (3.62; 5.14)	
FRC, % predicted	135 (125; 153)	
DLCO, mmol/min/kPa	4.58 (3.78; 6.92)	
DLCO, % predicted	58 (47; 77)	
$V'O_2$ max, L/min	1.24 (1.04; 1.46)	
$V'O_2$ max, % predicted	67 (54; 78)	
$V'O_2$ max, mL/min/kg	16.95 (14.55; 19.95)	
Comorbidities		
Arterial hypertension	13 (42)	
Coronary heart disease	4 (13)	
Diabetes	2 (6)	
Medications		
Inhaled β-adrenergics	23 (74)	
Inhaled anticholinergics	25 (81)	
Inhaled corticosteroids	17 (55)	
ACE inhibitor	5 (16)	
Beta-blocker	7 (23)	

Values are numbers of patients (% of group) or medians (lower quartile; upper quartile). RV, residual volume; FRC, functional residual capacity; DLCO, diffusing capacity.

Results

The patient selection flowchart is shown in Figure 1. From 40 randomized patients, 9 data sets had to be excluded, leaving 31 for the per-protocol analysis. No serious adverse events occurred, although 3 patients had an SpO_2 <80% before starting exercise and were therefore excluded from these tests. The patient characteristics are summarized in Table 1.

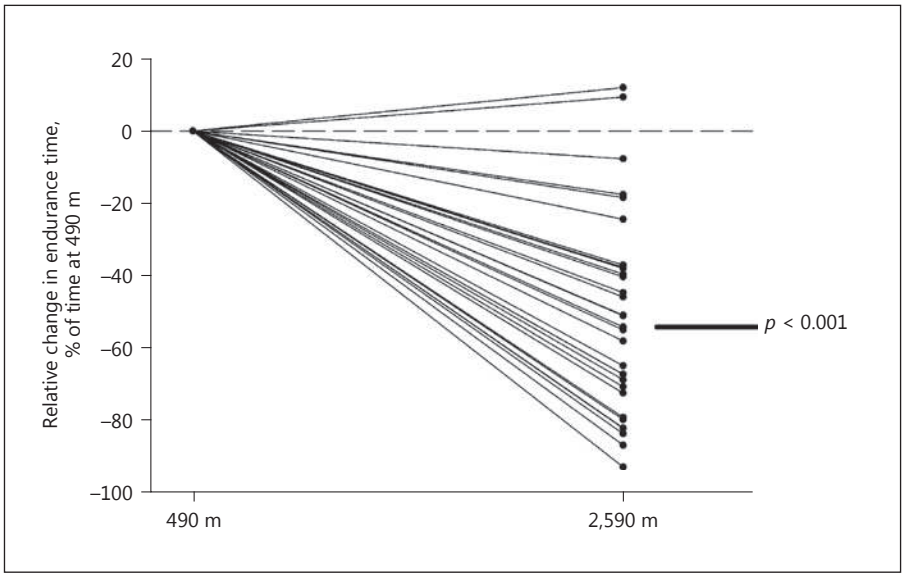

Fig. 2. Relative changes in endurance assessed by constant-load bicycle exercise in patients with COPD at 2,590 m compared to the baseline value at 490 m. Individual changes and the median change (horizontal line; reduction by 54%) are shown in percent of the baseline value at 490 m.

With ascent from 490 to 2,590 m, there was a significant reduction in exercise endurance time from a median (quartiles) of 500 s (256; 795) at 490 m to 205 s (139; 297) at 2,590 m, i.e., there was a median difference (95% CI) of –303 s (–420 to –150) corresponding to a mean relative change of –54% (–67 to –40) ($p < 0.001$) (Fig. 2). The numerical results are listed in Table 2, and a synopsis of the physiologic responses is provided in Figure 3.

Compared to 490 m, resting Pa_{O_2}, Sa_{O_2}, and Pa_{CO_2} were reduced at 2,590 m in association with an increased V'_E, breath rate, and ventilatory equivalents for oxygen uptake (V'_E/V'_{O_2}) and carbon dioxide output (V'_E/V'_{CO_2}) (Table 2; Fig. 3). Resting and end exercise CTO were also reduced at 2,590 m compared to 490 m, but the differences in MCAv and in MTO between the values at 490 m and those at 2,590 m, respectively, were not statistically significant (Fig. 3b, c).

During the final 30 s of end exercise at 2,590 m, V'_{CO_2} and, to a greater extent, V'_{O_2} were lower than the corresponding values at 490 m, so that the respiratory exchange ratio was increased at 2,590 m. At end exercise, V'_E, breath rates, and ventilatory equivalents were all elevated at 2,590 compared to 490 m (Table 2; Fig. 3). The adjusted ventilatory equivalents accounting for the lower P_B at 2,590 m were still slightly elevated over the values at 490 m with the exception of V'_E/V'_{CO_2} at end exercise (Table 2).

Breathing reserve, computed as $40 \times FEV_1 - V'_E$, was reduced more at 2,590 m than at 490 m. The EELVs increased significantly from rest to end exercise to a similar degree at both altitudes. The operational lung volumes (IRV and EILV) at end exercise were also similar at both altitudes (Tables 2, 3).

Pulse oximetry revealed a significant fall in Sp_{O_2} at rest and during exercise at 2,590 versus 490 m, and the exercise-induced drop in Sp_{O_2} was more pronounced at 2,590 m (Table 2; Fig. 3a). The arterial blood gas analysis at 2,590 m revealed a considerable exercise-induced fall in Pa_{O_2} and Sa_{O_2} from the resting values, and the Pa_{CO_2} at end exercise at 2,590 m was also reduced compared to the resting values. Calculation of the death space fraction ($V_D/V_T = [Pa_{CO_2} - Pet_{CO_2}]/Pa_{CO_2}$) revealed a reduction with exercise at both altitudes.

The heart rate and mean blood pressure at end exercise were similar at both altitudes. Despite a more pronounced exercise-induced arterial hypoxemia, a similar increase in MCAv was observed at both altitudes (Fig. 3e). The cerebral blood flow response to exercise-induced arterial hypoxemia, expressed as change in MCAv per change in Sp_{O_2}, was therefore lower at 2,590 m than at 490 m (Table 2; Fig. 3). CTO remained stable over the course of exercise at 490 m, but it decreased at 2,590 m to end exercise values lower than those at 490 m (Fig. 3b). MTO decreased with exercise at both altitudes (Fig. 3c).

Comparison of the values recorded at end exercise at 2,590 m with the corresponding values at isotime at 490 m revealed that the patients had a lower V'_{O_2} but a higher V'_E, respiratory exchange ratio, and heart rate at 2,590 m than at 490 m, and that they were more hypoxemic and had lower CTO and MTO at 2,590 m than at 490 m (Table

Table 2. Performance and physiologic response to exercise at 490 and 2,590 m

	490 m		2,590 m	
	rest	end exercise	rest	end exercise
Endurance, s	NA	500 (256; 795)	NA	205 (139; 297)*
V'_{O_2}, L/min	0.25 (0.20; 0.30)	1.01 (0.82; 1.23)*	0.26 (0.19; 0.33)	0.89 (0.64; 1.08)*, ¶
V'_{O_2}, % predicted V'_{O_2} max	15 (12; 16)	62 (50; 72)*	14 (12; 16)	50 (40; 61)*, ¶
V'_{CO_2}, L/min	0.22 (0.16; 0.24)	0.91 (0.69; 1.13)*	0.21 (0.15; 0.26)	0.88 (0.64; 1.07)*, ¶
Respiratory exchange ratio	0.80 (0.75; 0.84)	0.90 (0.84; 0.94)*	0.80 (0.75; 0.84	0.99 (0.90; 1.06)*, ¶
V'_E, L/min	12.2 (10.2; 14.1)	40.6 (35.5; 47.8)*	13.7 (12.4; 15.6)¶	47.2 (39.6; 58.7)*, ¶
Tidal volume, L	0.7 (0.5; 0.9)	1.2 (1.1; 1.7)*	0.7 (0.6; 0.9)	1.3 (1.1; 1.6)*
Breathing rate, *n*/min	20 (18; 23)	35 (31; 37)*	21 (18; 28)¶	36 (31; 42)*, ¶
Breathing reserve, L/min	55.4 (38.1; 76.1)	23.2 (11.9; 37.8)*	54.4 (37.7; 73.7)	17.6 (8.2; 26.5)*, ¶
Change in EELV, L	0	0.28 (0.06; 0.50)*	0	0.26 (0.05; 0.47)*
IRV, L	1.66 (1.10; 1.89)	0.95 (0.45; 1.24)*	1.52 (1.10; 1.83)	0.84 (0.63; 1.17)*
IRV/predicted TLC	0.15 (0.05; 0.26)	0.05 (–0.08; 0.16)*	0.12 (–0.01; 0.28)	0.02 (–0.11; 0.15)*
EILV/TLC	0.78 (0.72; 0.81)	0.86 (0.82; 0.92)*	0.78 (0.70; 0.82)	0.86 (0.82; 0.91)*
EILV/predicted TLC	0.85 (0.74; 0.95)	0.95 (0.84; 1.08)*	0.88 (0.72; 1.01)	0.98 (0.85; 1.11)*
V'_E/V'_{O_2}	37.5 (31.7; 42.2)	37.2 (30.7; 42.6)	42.6 (37.5; 53.0)¶	49.2 (42.1; 57.1)*, ¶
V'_E/V'_{O_2} adj. to P_B at 490 m	NA	NA	40.1 (35.9; 53.3)¶	41.2 (35.6; 49.3)¶
V'_E/V'_{CO_2}	46.9 (40.0; 50.9)	40.7 (34.2; 46.5)*	52.4 (49.2; 63.3)¶	49.7 (45.5; 55.5)*, ¶
V'_E/V'_{CO_2} adj. to P_B at 490 m	NA	NA	50.3 (44.7; 65.4)¶	42.4 (38.1; 47.4)
Pet_{CO_2}, kPa	3.8 (3.5; 4.0)	4.6 (4.0; 4.9)*	2.9 (2.2; 3.4)¶	3.3 (2.9; 3.5)*, ¶
V_D/V_T	0.33 (0.25; 0.36)	0.22 (0.11; 0.32)*	0.44 (0.30; 0.51)¶	0.27 (0.22; 0.37)*, ¶
Sp_{O_2}, %	95 (94; 96)	92 (89; 94)*	90 (86; 91)¶	81 (77; 84)*, ¶
Arterial pH	7.42 (7.40; 7.44)	7.38 (7.35; 7.41)*	7.45 (7.43; 7.46)¶	7.42 (7.39; 7.45)*, ¶
Pa_{CO_2}, kPa	5.6 (5.0; 6.0)	5.6 (5.5; 5.8)	5.0 (4.6; 5.2)¶	4.7 (4.3; 5.1)*, ¶
Pa_{O_2}, kPa	9.0 (8.4; 9.4)	8.3 (6.8; 8.7)	6.7 (6.3; 7.4)¶	5.8 (5.5; 6.5)*, ¶
Sa_{O_2}, %	94 (92; 95)	93 (92; 94)	85 (82; 89)¶	80 (75; 83)*, ¶
$DAaP_{O_2}$, kPa	5.6 (5.0; 6.8)	6.8 (5.7; 7.5)	3.0 (2.4; 3.4)¶	3.7 (2.8; 4.2)*, ¶
Heart rate, *n*/min	78 (72; 83)	122 (108; 130)*	81 (74; 91)	122 (107; 128)*
Heart rate reserve, *n*/min	78 (70; 85)	33 (24; 46)*	75 (62; 82)	34 (25; 47)*
Mean arterial BP, mm Hg	108 (99; 116)	138 (119; 157)*	113 (99; 120)	147 (126; 155)*
CTO, %	62 (59; 67)	62 (56; 66)	59 (55; 61)¶	55 (50; 60)*, ¶
MTO, %	68 (64; 71)	59 (53; 64)*	66 (64; 72)	53 (49; 64)*
MCAv, cm/s	47 (41; 56)	59 (51; 67)*	51 (45; 55)	62 (55; 67)*
MCAv response to hypoxia, %/%	NA	6 (3; 12)	NA	3 (2; 5)¶
Borg CR10 Scale score – dyspnea	0.5 (0; 1)	5 (4; 7)*	0 (0; 1)	7 (5; 8)*, ¶
Borg CR10 Scale score – leg fatigue	0 (0; 0.5)	4 (3; 6)*	0 (0; 1)	4 (2; 5)*

Total $n = 31$. Values are presented as medians (quartiles). Arterial blood gases were available at rest and during exercise for 31 and 10 patients at 490 m, respectively, and for all patients at 2,590 m. * $p < 0.05$ vs. rest at the corresponding altitude; ¶ $p < 0.05$ vs. the corresponding value at 490 m at rest or end exercise, respectively. V'_E, minute ventilation; V'_{O_2}, oxygen uptake; V'_{CO_2}, carbon dioxide output; V_D/V_T, dead space to tidal volume ration calculated as $V_D/V_T = [(Pa_{CO_2} - Pet_{CO_2})/Pa_{CO_2}]$ [12]; Pet_{CO_2}, end-tidal CO_2 partial pressure; Sp_{O_2} Sa_{O_2}, arterial oxygen saturation by pulse oximetry and by co-oximetry, respectively; EELV, end-expiratory lung volume; $DAaP_{O_2}$, alveolar-arterial P_{O_2} difference [28]; BP, blood pressure; MCAv, middle cerebral artery peak blood flow velocity; CTO, cerebral tissue oxygenation; MTO, muscle tissue oxygenation; MCAv response to hypoxia, % change in MCAv divided by corresponding % change in Sp_{O_2}; breathing reserve, computed as $40 \times FEV_1 - V'_E$ at end exercise; V'_E/V'_{CO_2} adj. and V'_E/V'_{O_2} adj. to P_B at 490 m, adjusted values that account for changes in barometric pressure of values expressed in BTPS (see Methods for explanation); IRV, inspiratory reserve volume; EILV, end-inspiratory lung volume.

3). The Borg CR10 Scale dyspnea but not leg fatigue ratings at end exercise were increased at 2,590 versus 490 m.

Multivariate regression analysis with endurance at 2,590 m as the (log-transformed) dependent variable revealed that altitude (coefficient [95% CI] –0.452 [–0.558 to –0.347]; $p < 0.001$), baseline endurance (coefficient 0.0007 [0.0005–0.0008]; $p < 0.001$), and baseline FEV_1 % predicted (coefficient 0.014 [0.006–0.022]; $p = 0.001$) were significant independent predictors, whereas the order of altitude exposure (coefficient 0.083 [–0.019 to

Table 3. Physiologic response to exercise at 490 and 2,590 m at isotimes

	490 m	2,590 m
Endurance, s	205 (139; 297)	205 (139; 297)
V'_{O_2}, L/min	0.93 (0.78; 1.14)*	0.90 (0.64; 1.08)*,¶
V'_{O_2}, % predicted V'_{O_2} max	56 (48; 68)*	50 (41; 61)*,¶
V'_{CO_2}, L/min	0.83 (0.65; 1.06)*	0.88 (0.64; 1.07)*
Respiratory exchange ratio	0.91 (0.84; 0.93)*	0.99 (0.90; 1.06)*,¶
V'_E, L/min	34 (31; 43)*	47.5 (39.6; 58.7)*,¶
Tidal volume, L	1.3 (1.1; 1.8)	1.4 (1.1; 1.8)*
Breathing rate, *n*/min	28 (23; 32)*	36 (31; 42)*,¶
Breathing reserve, L/min	28.0 (17.2; 49.0)*	18.7 (8.3; 35.2)*,¶
Change in EELV, L	0.27 (0.13; 0.49)	0.12 (0.00; 0.63)
IRV, L	0.81 (0.34; 1.18)*	0.84 (0.62; 1.17)*
IRV/predicted TLC	0.05 (–0.09; 0.16)*	–0.01 (–0.13; 0.15)*
EILV/TLC	0.87 (0.83; 0.94)*	0.86 (0.82; 0.91)*
EILV/predicted TLC	0.95 (0.84; 1.09)*	1.01 (0.85; 1.13)*
V'_E/V'_{O_2}	36 (29; 40)	49 (42; 57)*,¶
V'_E/V'_{O_2} adj. to P_B at 490 m	NA	41 (36; 49)
V'_E/V'_{CO_2}	40 (34; 43)*	50 (45; 55)*,¶
V'_E/V'_{CO_2} adj. to P_B at 490 m	NA	42 (38; 47)*
Sp_{O_2}, %	93 (89; 95)*	81 (77; 84)*,¶
Heart rate, *n*/min	109 (103; 119)*	122 (107; 128)*,¶
Heart rate reserve, *n*/min	47 (32; 54)*	35 (25; 47)*,¶
Mean arterial BP, mm Hg	136 (126; 148)*	149 (126; 158)*,¶
CTO, %	62 (57; 65)	55 (50; 60)*,¶
MTO, %	58 (53; 65)*	53 (48; 64)*,¶
MCAv, cm/s	59 (52; 70)*	62 (52; 67)*
MCAv response to hypoxia, %/%	3 (1; 7)	2 (1; 2)

Isotime refers to the time of end exercise in the test with the shorter endurance. In 29 of 31 instances, this was the test at 2,590 m (see Fig. 2). Values are presented as medians (quartiles). * $p < 0.05$ vs. rest at the corresponding altitude; ¶ $p < 0.05$ vs. isotime at 490 m. V'_{O_2}, oxygen uptake; V'_{CO_2}, carbon dioxide output; Sp_{O_2}, arterial oxygen saturation by pulse oximetry; EELV, end-expiratory lung volume; BP, blood pressure; MCAv, middle cerebral artery peak blood flow velocity; CTO, cerebral tissue oxygenation; MTO, muscle tissue oxygenation; MCAv response to hypoxia, % change in MCAv divided by corresponding % change in Sp_{O_2}; breathing reserve, computed as $40 \times FEV_1 - V'_E$ at end exercise; V'_E/V'_{CO_2} and V'_E/V'_{O_2} adj. to P_B at 490 m, adjusted values that account for changes in barometric pressure in values expressed in BTPS (see Methods for explanation); IRV, inspiratory reserve volume; EILV, end-inspiratory lung volume.

0.184]; $p = 0.112$), baseline Sp_{O_2} (coefficient –0.014 [–0.074 to 0.045]; $p = 0.633$), and lung diffusing capacity (coefficient –0.409 [–1.062 to 0.245]; $p = 0.220$) were not ($R^2 = 0.7603$; $p < 0.0001$).

Discussion

The main finding of the current randomized trial on lowlanders with moderate-to-severe COPD (GOLD grades 2–3) was a major reduction in endurance by 54% during constant-load bicycle exercise at 2,590 m compared to baseline values at 490 m. The performance decrements at 2,590 m were associated with arterial hypoxemia, deoxygenation of muscle and cerebral tissues, and an impaired cerebral blood flow response to the exercise-induced decline in Sp_{O_2}. The breathing reserve was reduced more at 2,590 m than at 490 m, with associated higher ventilatory equivalents for V'_{CO_2} and V'_{O_2} and a similar degree of dynamic hyperinflation. Therefore, the greater degree of dyspnea and impairment in exercise performance that lowlanders with COPD experience at moderate altitude is multifactorial, likely involving impairments in systemic and cerebral availability of oxygen as well as in pulmonary gas exchange.

In 51 healthy young men ascending from 490 to 2,590 m within a few hours, we previously observed a decrease in resting Sp_{O_2} from 95 to 91% associated with a decrease

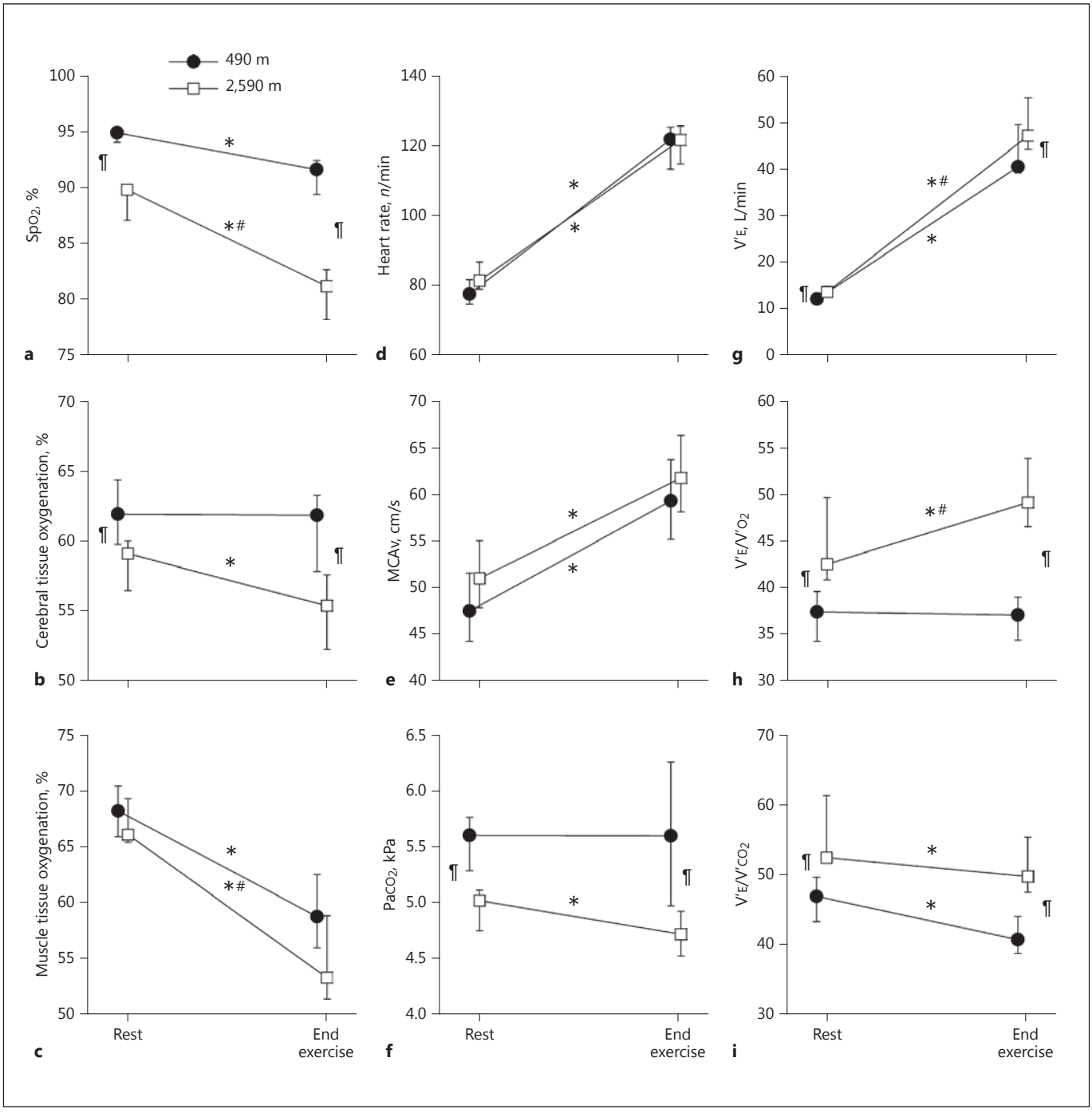

Fig. 3. Changes in physiologic variables from rest to end exercise at 490 m and 2,590 m shown as medians and interquartile ranges. **a** Pulse oximetry (SpO_2). **b** Cerebral tissue oxygenation. **c** Muscle tissue oxygenation. **d** Heart rate. **e** Middle cerebral artery peak blood flow velocity (MCAv). **f** $PaCO_2$. **g** Minute ventilation (V'_E). **h** Ventilatory equivalent for oxygen (V'_E/V'_{O_2}). **i** Ventilatory equivalent for carbon dioxide (V'_E/V'_{CO_2}). * $p < 0.05$ vs. rest at corresponding altitude; ¶ $p < 0.05$ vs. corresponding value at 490 m at rest or end exercise, respectively; # $p < 0.05$ for comparison of corresponding exercise-induced changes from rest to end exercise at 2,590 vs. 490 m.

in end-tidal P_{CO_2} (the surrogate of Pa_{CO_2}) from 5.3 to 4.8 kPa [24]. This was consistent with an increase in ventilatory drive, and thus alveolar ventilation, induced by the hypobaric hypoxia. Exercise tests were not performed in that study. Investigations in 8 elite cyclists at sea level and after 1 day of exposure to 2,340 m revealed a decrease in W_{max} by 14%, in V'_{O_2} max by 13%, and in maximal cycling endurance by 26% at a constant load of 80% of the sea level W_{max} [25]. Similar data on the physiologic effects of altitude on COPD patients have not been available. One uncontrolled case study on 18 COPD patients (mean FEV_1 42% predicted) ascending within 2–3 h from sea level to 2,086 m revealed a reduction in 6-min walk distance within 1 h after arrival at 2,086 m by 52% in association with drops in Sp_{O_2} to 75% [26]. The participants in the current study had a slightly higher FEV_1 (56% predicted) (Table 1) than those in the cited study, but they were exposed to a higher altitude of 2,590 m, which may explain the similar reduction in exercise endurance by 54% of the value at 490 m. Differences in timing and type of exercise hamper further comparisons between the two studies. To our knowledge, the current randomized trial for the first time provides quantitative data on reductions in exercise performance and the underlying physiologic mechanisms in lowlanders with COPD travelling to moderate altitude.

Our data recorded at low altitude (490 m) are consistent with those of previous studies showing a reduced breathing reserve and exercise-induced hypoxemia in patients with severe COPD [27]. Although the breathing reserve of the patients in the current study was not exhausted at either of the two altitudes, it was reduced more at 2,590 m than at 490 m (Table 2), most likely due to hypoxic ventilatory stimulation and because of the more pronounced ventilatory inefficiency for V'_{O_2} and V'_{CO_2} at 2,590 m. The increases in ventilatory equivalents for V'_{CO_2} and V'_{O_2} were mainly due to the reduced P_B, since increases in these variables after adjustment for changes in gas density at 2,590 m were minor. Thus, the effects of altitude-related changes in Pa_{CO_2} and alveolar P_{CO_2} and of V_D/V_T on V'_E/V'_{CO_2} seemed to be small. The exercise-induced increase in alveolar-arterial P_{O_2} difference [28] at 2,590 m may have contributed to the increased V'_E/V'_{O_2}. Despite the higher V'_E at end exercise at 2,590 m, dynamic hyperinflation was not greater than that at 490 m, which is possibly related to the reduced air density and its effect on airflow resistance at the higher altitude [29], even though FEV_1 and FEV_1/FVC were similar at 2,590 and 490 m. Consistently, IRV and EILV at end exercise were similar at both altitudes, suggesting that the higher V'_E at 2,590 m was not associated with higher operational lung volumes. Therefore, the impairment in exercise performance and excessive dyspnea in COPD patients travelling to high altitude were more likely due to a reduced oxygenation of the brain than to mechanical ventilatory constraints. In terms of clinical implications, these findings may suggest that the reduced exercise endurance of COPD patients at higher altitudes might be alleviated by oxygen supplementation rather than by pharmacological bronchodilation.

The reduced inspiratory P_{O_2} at 2,590 m exacerbated the hypoxemia at rest and during exercise, despite the hypoxic stimulation of V'_E that was reflected in a lower Pa_{CO_2} at 2,590 m. In healthy subjects, cerebral deoxygenation recorded by NIRS during exposure to a high simulated altitude was associated with reduced exercise performance [30]. These data and improvements in CTO and exercise performance with oxygen supplementation at high altitude suggest a role of cerebral hypoxia in exercise limitation [31, 32]. In the current study on COPD patients, CTO remained stable throughout the exercise tests at 490 m. However, CTO dropped significantly at 2,590 m (Table 1; Fig. 3). Moreover, the response of cerebral blood flow to hypoxemia was reduced, possibly related to hypocapnia-induced cerebral vasoconstriction at 2,590 m [33]. Cerebral hypoxia may therefore have contributed to exercise limitation in the COPD patients at 2,590 m. In contrast to CTO, MTO was similar at end exercise at both altitudes, suggesting that impairment of MTO was not a main factor in the reduced performance at 2,590 m.

Heart rates at end exercise were similar at both altitudes. Presumably, a further augmentation of the cardiovascular response to exercise at 2,590 m was prevented by premature termination of exercise due to pronounced dyspnea. Alternatively, hypoxemia may have restricted the maximal heart rate during exercise at 2,590 m, as observed in some studies on healthy individuals acutely exposed to hypoxia [34], although another report suggested that a decrease in maximal heart rate occurred only after several days of acclimatization at high altitude [35]. Hypobaric hypoxia has been associated with elevation of pulmonary artery [2] and systemic blood pressures [36].

In terms of the clinical relevance of our findings, it is important to note that despite performing physical work to exhaustion, none of the patients with a severity grade of COPD (GOLD 2–3) that usually allows still being active and considering travel experienced a serious adverse event. The selected study altitude of 2,590 m is of particular interest, because it is similar to altitudes visited during

recreational walking or skiing and not far off the maximal cruising altitude equivalent permitted in commercial air flights (8,000 ft or 2,438 m). The results are therefore reassuring for COPD patients considering travelling at moderately high altitudes or air travel.

Conclusions

In conclusion, our results demonstrate that COPD patients travelling to moderate altitudes experience a considerable limitation of exercise performance that seems relevant to activities of daily life. The results of the comprehensive physiologic evaluation performed in the current study are consistent with a reduced exercise performance due to combined adverse effects of hypobaric hypoxia on dyspnea, pulmonary gas exchange, and cerebral hypoxia. These data may help to counsel patients with COPD planning high-altitude travelling.

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Author Contributions

M.F.: guarantor of the paper. M.F. and K.E.B.: contribution to the conception and design of the study; the collection, analysis, and interpretation of the data; and the writing of the manuscript. T.D.L. and S.U.: conception and design of the work, and acquisition, analysis, and interpretation of the data. S.E.H., D.F., P.M.S., C.M., B.O., M.J.P., and M.K.: acquisition, analysis, and interpretation of the data, and revision of the manuscript.

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